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Multidisciplinary treatment of advanced hepatocellular carcinoma with severe arterioportal shunt: a case report

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Abstract

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer mortality globally. In addition, most patients present in advanced stages with limited curative treatment options. Therefore, multidisciplinary treatment is often warranted. Here, we report a patient with HCC and severe arterioportal shunt (APS) who was treated with a multidisciplinary approach comprising interventional radiology procedures, apatinib and camrelizumab. After treatment, the intrahepatic mass was stable, and a notable decrease in the number and size of lung lesions was observed. The patient achieved a long-term survival of more than 2 years. These data suggest that multidisciplinary treatments may be effective in the treatment of advanced HCC with severe APS.

Keywords

Multidisciplinary treatment, hepatocellular carcinoma, arterioportal shunt, advanced stage, interventional radiology, apatinib, camrelizumab

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Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related death worldwide.[1] Furthermore, most patients are diagnosed with unresectable or advanced stage disease with limited curative treatment options.[2] Therefore, novel

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therapeutic strategies for patients with unresectable or advanced HCC are urgently required. In this report, we describe the case of a patient with advanced HCC and severe intratumoral arterioportal shunt (APS) who showed a favorable response following multidisciplinary treatment, including interventional radiology procedures, apatinib and camrelizumab.

Case presentation

A 31-year-old man who suffered from chronic hepatitis B virus-associated liver cirrhosis for 10 years presented to another hospital with hematemesis. He was then diagnosed with HCC and severe intratumoral APS, which caused portal hypertension leading to esophagogastric variceal bleeding (Figure 1). Thereafter, he underwent endoscopic variceal ligation, followed by endoscopic injection sclerotherapy three times. Despite these treatments, the esophagogastric varices deteriorated further. The patient was then referred to our hospital on 19 November 2018 for further treatment. Magnetic resonance images showed similar findings to the outside hospital computed tomography (CT) scan. No chest CT scan was available, but chest X-ray examination revealed no abnormalities. Preoperative biochemical examinations showed that the alpha–fetoprotein (AFP) level exceeded 2000 ng/mL (normal range: 0–8 ng/mL), which was the upper limit at our laboratory. The other parameters were as follows: hemoglobin = 78 g/L, total bilirubin = 13.4 μmol/L, albumin = 41 g/L, prothrombin time = 15.5 s and creatinine = 55 μmol/L. The patient's Child–Pugh score was six (Class A), and the model for end-stage liver disease score was nine. The patient was classified by the Barcelona Clinical Liver Cancer (BCLC) system as stage B. The BCLC treatment algorithm recommended transarterial chemoembolization (TACE) over surgical resection, radiofrequency ablation and other therapeutic options.

Because severe APS causes portal hypertension that leads to esophagogastric variceal bleeding, transjugular intrahepatic portosystemic shunt (TIPS) and APS embolization were performed to reduce the risk of rebleeding. Hepatic angiography using a 5F catheter (Terumo Corporation, Tokyo, Japan) revealed a marked APS communication between the left hepatic artery and the left branch of the portal vein, accompanied by reflux into the main portal vein (Figure 2). The left hepatic artery was occluded with multiple coils and gelatin sponge particles through a 2.7F microcatheter (Progreat, Terumo, Japan) to reduce blood flow through the APS. Subsequently, TIPS using two self-expandable stents (8×100 mm and 8×80 mm each, Angiomed GmbH & Co., Karlsruhe, Germany) was performed (Figure 2), followed by embolization of the esophagogastric varices with a mixture composed of Histoacryl and iodized oil (B. Braun, Melsungen, Germany). The technique was completed without procedure-related complications. After the procedure, the portal pressure in direct measurements decreased from 50 cm H_2O to 40 cm H_2O.

Despite the TIPS operation, the portal pressure did not substantially improve. Given this, TACE was performed again to reduce blood flow through the APS on 17 December 2018. Embolization with coils and polyvinyl alcohol particles (Hangzhou Alicon Pharm SCI & TEC Co., Ltd., Zhejiang, China) was initially performed to occlude the shunt, followed by infusion of a small amount of iodized oil and 10 mg pirarubicin emulsion (Shenzhen Main Luck Pharmaceuticals Inc., Shenzhen, China). After the procedure, repeated hepatic arteriography showed that the APS was reduced but still present.

The patient had an uneventful recovery after TIPS and TACE. On 24 December

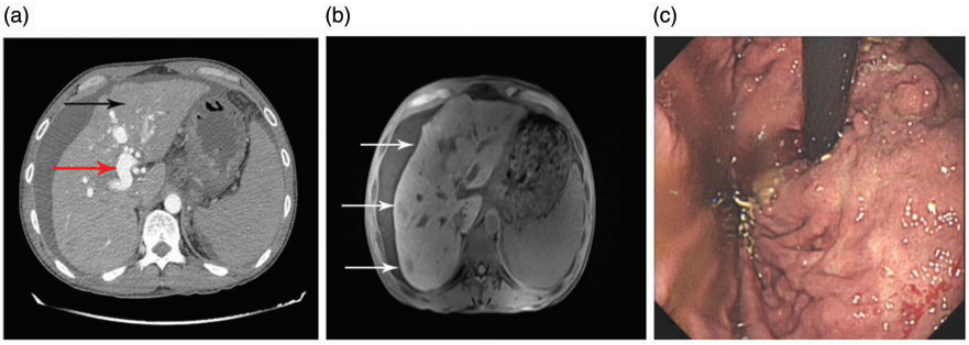

Figure 1. Contrast-enhanced CT, MRI and upper gastrointestinal endoscopy findings in a 31-year-old man with hepatocellular carcinoma and severe APS. (a) CT showed a huge mass measuring approximately 7 cm in diameter in the left hepatic lobe (black arrow). The lesion was unenhanced in the arterial phase because the tumorous APS reduced arterial blood flow. A hyper-enhanced portal vein was present in the arterial phase CT image (red arrow). CT images also identified ascites and splenomegaly. (b) MRI in our hospital showed multiple hypodense parenchyma masses (white arrows, liver segment 4,5,6), similar to the outside hospital CT scan. (c) Upper gastrointestinal endoscopy revealed severe esophagogastric varices.
CT, computed tomography; MRI, magnetic resonance images; APS, arterioportal shunt.

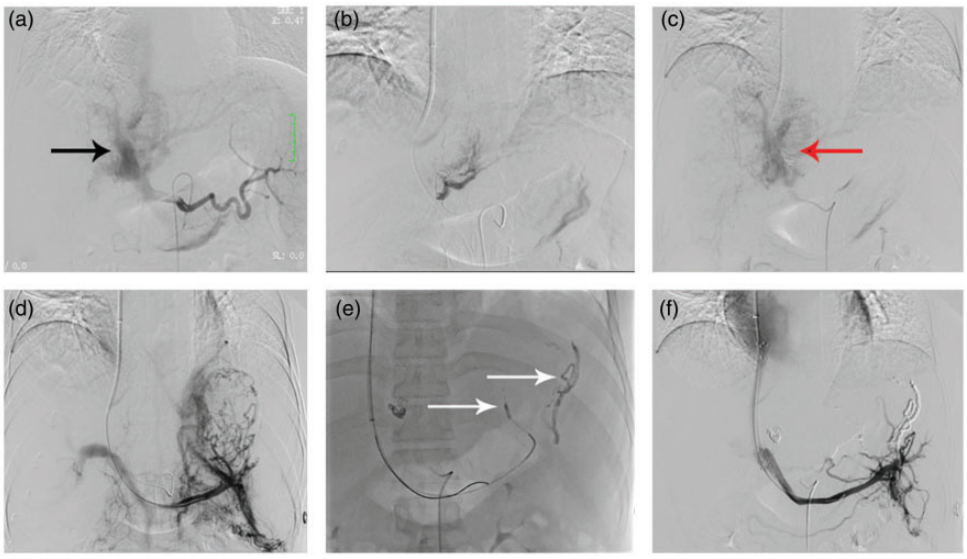

Figure 2. Hepatic angiography in the patient reported in this case. (a) Hepatic angiography shows a marked APS communication between the left hepatic artery and the left branch of the portal vein accompanied by reflux into the main portal vein (black arrow). (b) Left hepatic artery angiogram demonstrates tumor staining. The tip of the microcatheter was placed in a feeding artery. (c) Post-embolization shows part occlusion of the APS by multiple coils (red arrow) and gelatin sponge particles. (d) Major findings of portal vein angiography during TIPS. (e) Embolization of the gastric varices with a mixture composed of Histoacryl and iodized oil (white arrows). (f) Portogram obtained immediately after TIPS creation shows good passage of the contrast medium through the shunt.
APS, arterioportal shunt; TIPS, transjugular intrahepatic portosystemic shunt.

2018, he was discharged from the hospital with close follow-up.

The patient was re-hospitalized to undergo TACE on 22 January 2019, and molecular targeted therapy with apatinib was started (250 mg orally once daily). Shortly after the initiation of apatinib treatment, he suffered from hematemesis (Common Terminology Criteria Adverse Events version 5.0, grade 3). Complete hemostasis was obtained after apatinib therapy was interrupted. On 28 May 2019, CT scans showed enlarged tumors in the liver with lung metastases, and the serum AFP level increased to 1256 ng/mL.

With careful consideration and the patient's informed consent, we initiated immunotherapy with camrelizumab. Camrelizumab 200 mg was administered intravenously over 30 minutes once every 2 weeks in a 4-week cycle. The patient tolerated the infusion without any complications. After another three cycles of therapy, the follow-up CT scans showed stable hepatic lesions and a continuous decrease in the size of lung lesions (Figure 3). However, camrelizumab therapy was discontinued because of an economical issue.

Subsequently, TIPS revision and two sessions of TACE were performed. The latest follow-up CT showed that the tumor burden had decreased, the severe APS was relieved, and most lung lesions had diminished in size or disappeared. However, he passed away on 27 December 2020 (3 months after the last visit). The full clinical course of this patient assessed by AFP levels and therapeutic events is shown in Figure 4.

Discussion

In this article, we reported a patient with advanced HCC and APS undergoing multidisciplinary treatment, including interventional radiology procedures, apatinib and camrelizumab. To the best of our knowledge, such a case has not been previously documented.

HCC combined with APS is a common phenomenon in clinical practice. APS has been reported in 28.8% to 63.2% of HCC cases.[3] Severe APS aggravates the complications of portal hypertension, diminishes the efficacy and safety of TACE and potentially promotes lung metastases. Portal hypertension arising from APS leads to the rupture of gastroesophageal varices, which is a life-threatening complication. Therefore, it is essential to treat severe APS for these patients. Endovascular embolization remains the treatment of choice. Several studies have suggested that TACE with various embolic agents, such as coils, ethanol, polyvinyl alcohol and gelatin sponge, is an effective treatment.[4,5] Here, we used coils combined with gelatin sponge or polyvinyl alcohol particles to embolize the severe APS. Subsequently, routine TACE was performed if there were residual tumor feeders after embolization. Unfortunately, APS was relieved but resistant to two TACE procedures. For the treatment of esophagogastric variceal bleeding as a result of portal hypertension, endoscopic treatment is the standard therapy and has been performed in multiple studies with some degree of success.[6] However, in our case, endoscopic treatment was usually insufficient to eradicate the varices and failed to control the esophagogastric variceal bleeding. TIPS is used as a second-line therapy to reduce the hepatic venous pressure gradient, resulting in portal venous decompression and variceal bleeding control. In the presented case, we performed TIPS in combination with endovascular embolization of the APS to decrease portal hypertension. After TIPS creation and APS embolization, the portal pressure decreased from 50 cm H_2O to 40 cm H_2O. The patient remained stable for the rest of the hospital stay with no signs of recurrent bleeding. The result suggested

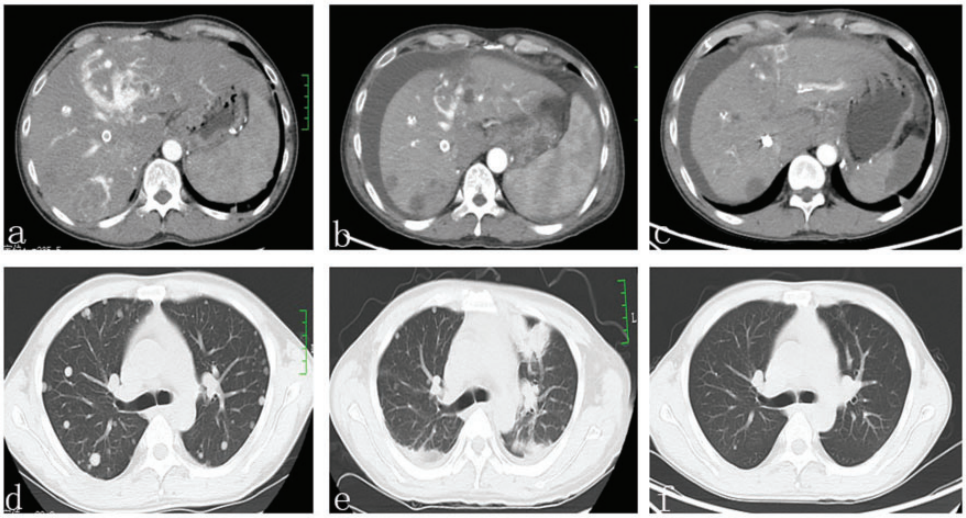

Figure 3. Contrast-enhanced CT before and after camrelizumab therapy. CT images before treatment with camrelizumab (a, d) and after two cycles (b, e) and four cycles (c, f) of camrelizumab (200 mg administered intravenously over 30 minutes once every 2 weeks in a 4-week cycle). A CT image shows hepatocellular carcinoma with APS and multiple bilateral lung metastases (a, d). All lung lesions rapidly responded to camrelizumab (b, e), and after four cycles, most lesions were diminished in size or had disappeared. Liver masses remained stable, and APS was relieved (c, f).
CT, computed tomography; APS, arterioportal shunt.

that our treatment strategy was effective and did not cause major complications.

In patients with BCLC stage B, palliative locoregional treatments, such as TACE, remain the gold standard for therapy. However, the initiation of systemic therapy is recommended if no response is observed after 1 or 2 TACE sessions or progression with extrahepatic spread is detected.[7] In the present case, the patient was initially treated with interventional treatment alone. Unfortunately, the tumor and APS were not well controlled, and extrahepatic metastasis emerged. Under this condition, the treatment strategy was switched from locoregional treatment to systemic therapy. Therefore, we performed multidisciplinary treatment, including molecular targeted therapy and immunotherapy.

Molecular targeted therapy is a topic of high interest in the multidisciplinary treatment of HCC. Various molecular targeted drugs for advanced HCC have been developed. Lenvatinib is currently feasible as a first-line treatment for advanced HCC. Regorafenib, cabozantinib and ramucirumab have also been recommended as second-line treatment options.[8] A previous study reported that a patient with initially unresectable HCC and obvious APS achieved conversion hepatectomy after lenvatinib treatment.[9] However, there are limited data on apatinib, a novel highly selective vascular endothelial growth factor (VEGFR)-2 tyrosine kinase inhibitor developed in China, for the treatment of HCC. For this case, we attempted to administer molecular targeted therapy with 250 mg apatinib once daily. The intrahepatic mass was stable, and a gradual decrease in AFP after apatinib therapy was observed. Unfortunately, he suffered

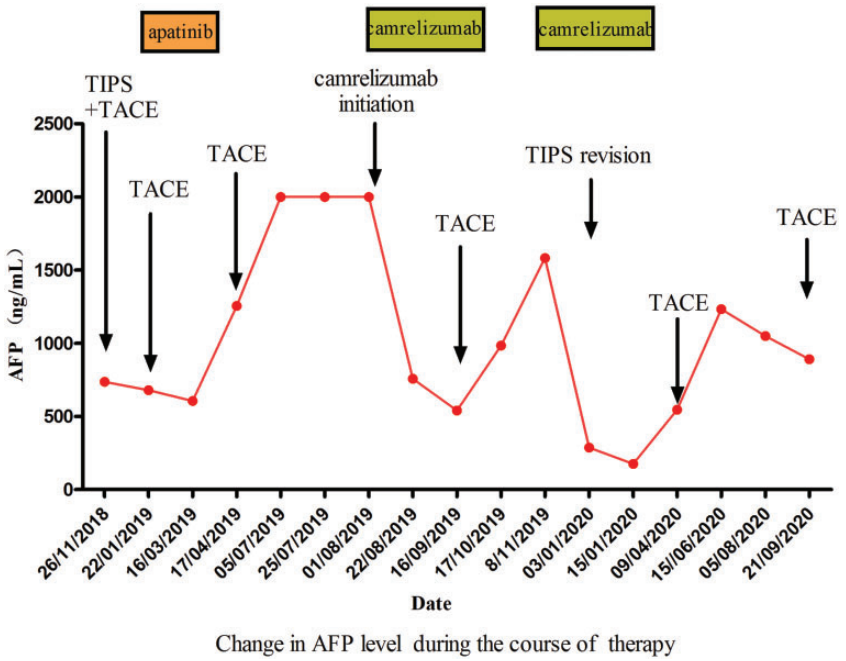

Figure 4. Clinical course of the patient reported in this case assessed by AFP levels and therapeutic events. Molecular targeted therapy with apatinib (250 mg) was administered orally once daily. Camrelizumab (200 mg) was administered intravenously over 30 minutes once every 2 weeks in a 4-week cycle.
AFP, alpha–fetoprotein; TIPS, transjugular intrahepatic portosystemic shunt; TACE, transarterial chemoembolization.

hematemesis, and apatinib was discontinued.

Recently, cancer immunotherapies have attracted increasing attention as potential clinical treatments, particularly for patients with late-stage disease. A major breakthrough was the development of antibodies targeting negative regulators of T-cell activation known as immune checkpoints. Immune checkpoint inhibitors restore the cytotoxic ability of T cells to destroy tumor cells by blocking the programmed death (PD)-1 receptor. Moreover, targeted inhibition of the PD-1 checkpoint significantly increases the antitumor efficacy of T cells. Thus, anti-cancer immunity is enhanced by antibodies that block the PD-1/programed death-ligand 1 (PD-L1) interaction. Immune checkpoint inhibitors have been extensively studied in multiple tumors, including HCC.[10] Camrelizumab (HENGRUI MEDICINE Co, Ltd. Jiangsu, China) is a monoclonal antibody that inhibits PD-1 immune checkpoint signaling. In a recent camrelizumab trial, 32 of 217 (14.7%) patients with previously treated advanced HCC experienced an objective response with tolerable adverse effects, and the 6-month overall survival probability was 74.4%.[11] In this case, the patient exhibited a promising clinical response to camrelizumab therapy. After the administration of camrelizumab, stable condition of the intrahepatic mass, a notable decrease in the number and size of lung lesions and a significant decline in AFP levels were observed (Figure 3 and Figure 4). We speculated that two or more

cycles of camrelizumab treatment were significantly associated with an objective response. Based on the promising evidence from the camrelizumab trial, the China National Medical Products Administration officially approved camrelizumab as a second-line treatment for advanced HCC patients.

Notably, recent clinical data revealed that immunotherapy combined with molecular targeted therapy might achieve synergetic effects. Liang et al.[12] reported that patients who received PD-1 blockade-activated multiple antigen-specific cellular therapy in combination with apatinib showed a significant improvement in progression-free survival. Xu et al.[13] showed that a combination of camrelizumab and apatinib achieved high objective response rates, durable responses and long-term survival in patients with advanced HCC in both the first-line and second-line settings. Yuan and his colleagues found that camrelizumab and apatinib obtained a favorable outcome in patients with advanced HCC who developed tumor thrombus.[14] These promising results may be due to the normalization of the tumor microenvironment. The VEGF/VEGFR pathway plays an important role in the regulation of the tumor microenvironment immune status. The inhibition of VEGFR2 by apatinib has immunomodulatory effects mediated by a reduced number and function of regulatory T cells and myeloid-derived suppressor cells and enhanced dendritic cell maturation and effector T cell mobilization, activation and infiltration. As a result, the immunosuppressive tumor microenvironment is reprogrammed into an immunostimulatory microenvironment, ultimately reducing its immunosuppressive effects and suppressing tumor growth.[15] Therefore, in line with these studies, although apatinib administration was interrupted in our case, it is reasonable to hypothesize that the tumor microenvironment was altered by apatinib, enabling improved responses to the immune checkpoint blockade. Taken together, synergism between immunotherapy and molecular targeted therapy provides a rationale for the development of camrelizumab and apatinib combination therapy. Camrelizumab alone or in combination with apatinib may also be an option for the treatment of advanced HCC. Unfortunately, the patient passed away 3 months after the last visit. We speculate that the patient died from disease progression because he was at an advanced tumor stage and missed follow-up for the last three months. Therefore, close follow-up is needed.

Conclusion

HCC is a complex disease that requires a multidisciplinary treatment strategy. The results obtained from our case demonstrated promising tumor control with multidisciplinary treatment in a patient with advanced HCC. Multidisciplinary treatments, including interventional radiology procedures, molecular targeted therapy and immunotherapy, may be an effective treatment option for advanced HCC accompanied by severe APS. However, further studies are needed to confirm our findings.

Ethics statement

Written informed consent of all treatment procedures was obtained from the patient and his wife. The reporting of this study conforms to CARE guidelines.[16] This case report was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi University of Chinese Medicine (approval number: 2018-034-02). A signed consent form for the publication of this case was obtained from the patient's wife.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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